




DEPARTMENT OF HEALTH AND HUMAN SERVICES

Office of the Secretary

Assistant Secretary for Health
Office of Public Health and Science
Washington D.C. 20201

DATE: January 29, 2001

TO: Interested Parties

FROM: Stephen D. Nightingale, MD 
Executive Secretary, Advisory Committee on Blood Safety and Availability

SUBJECT: January 26, 2001 Recommendations of the Advisory Committee

At the above-referenced meeting, the Advisory Committee made the following six recommendations:

1. Universal leukoreduction should be implemented as soon as feasible.
2. In regard to universal leukoreduction, the Advisory Committee is concerned about the availability of blood, and the resources necessary to implement universal leukoreduction. For these reasons, the Advisory Committee recommends that the actions of the Department of Health and Human Services should strive to
 - a. minimize the impact on supply,
 - b. assure adequate funding for this effort,
 - c. issue a regulation to implement universal leukoreduction that addresses these concerns, and
 - d. report to the Advisory Committee on a regular basis the progress toward these goals.
3. The Advisory Committee recommends that the Secretary appoint a representative of the Health Care Financing Administration as a non-voting government representative to the Advisory Committee.
4. Given the unresolved scientific issues in the field, the Advisory Committee supports continuing research on the effectiveness of universal leukoreduction.
5. In the above resolutions, the word "leukoreduction" is intended to mean prestorage leukoreduction, and the resolutions refer to non-leukocyte cellular blood components.
6. The Advisory Committee extends its congratulations and best wishes to its member Dr. Dana Kuhn, his wife, and their family on the occasion of the birth on January 22, 2001 of Krysten Marie Kuhn and Josef Weber Kuhn.



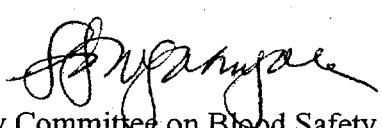
DEPARTMENT OF HEALTH AND HUMAN SERVICES

Office of the Secretary

Assistant Secretary for Health
Office of Public Health and Science
Washington D.C. 20201

DATE: February 1, 2001

TO: Interested Parties

FROM: Stephen D. Nightingale, MD 
Executive Secretary, Advisory Committee on Blood Safety and Availability

SUBJECT: Summary of January 25 and 26, 2001 Meeting

The Advisory Committee on Blood Safety and Availability met for the thirteenth time on January 25 and 26, 2001 at the Hyatt Regency Capitol Hill Hotel, 400 New Jersey Ave., NW, Washington, DC 20001 to consider how the government should respond to the current public debate over universal leukoreduction. Voting members present were Dr. Caplan, the Chairman; Mr. Allen; Dr. Busch; Mr. Dalal; Drs. Davey, Gilcher, Gomperts, Haas, and Hoots; Ms. Lipton; Dr. Lopes; Ms. Pahuja; Drs. Penner and Piliavin; and Mr. Walsh. Non-voting government members present were Drs. Chamberland and Epstein; COL FitzPatrick; and Drs. McCurdy and Snyder. Also present were Dr. Nightingale, the Executive Secretary; CAPT McMurtry, the Deputy Executive Secretary; and approximately 150 members of the public.

As the meeting opened Dr. Davey proposed, and Dr. Epstein seconded, the following motion:

The Advisory Committee extends its congratulations and best wishes to its member Dr. Dana Kuhn, his wife, and their family on the occasion of the birth on January 22, 2001 of Krysten Marie Kuhn and Josef Weber Kuhn.

The motion was approved unanimously.

Dr. David Sacher, the Surgeon General and Acting Secretary of Health and Human Services, welcomed Mr. Dalal and Dr. Lopes to the Advisory Committee, thanked Mr. Allen, Dr. Gomperts, and Dr. Penner for agreeing to serve an additional term, and thanked Drs. AuBuchon and Secundy for their previous service. He expressed his support for donor recruitment programs titled "My Blood, Your Blood" (America's Blood Centers) and "It's What's Inside That Counts" (American Red Cross), and welcomed Dr. Jean Emmanuel of the World Health Organization as an observer to the meeting. Dr. Satcher outlined the agenda for the meeting, and concluded by thanking all the Advisory Committee members for their many contributions.

Dr. Epstein summarized FDA's prior actions related to universal leukoreduction, including the publication of a Guidance to Industry on January 23, 2001. He specifically requested that the Advisory Committee comment on the issue of reimbursement as it affects the opportunities for blood safety advances, both in relation to leukoreduction and to future advances.

The Advisory Committee then heard invited presentations on universal leukoreduction from a panel of experts in transfusion medicine. The panel was moderated by Drs. Morris Blajchman and Eleftherios Vamvakas.

Dr. Harvey Klein opened his discussion by pointing out that current prestorage leukoreduction filters can prevent over 90% (but not all) febrile transfusion reactions, reduce HLA alloimmunization to donor leukocyte antigens, and lessen exposure to certain cell-associated pathogens like CMV. He noted that transfusions can suppress some immune reactions and, by adoptive transfer of lymphocytes, induce others (such as graft-versus-host disease in certain immunosuppressed recipients). However, he cautioned that some proposed effects of transfused lymphocytes on postoperative infections, recurrence of certain cancers, and overall mortality have not yet been conclusively demonstrated. He also noted that leukoreduction removes about 10% of red cells from the filtered unit, and that blood donations by individuals with sickle cell disease can not be filtered efficiently.

Dr. Edward Snyder described his experience with universal leukoreduction at Yale-New Haven Hospital, where about 45,000 blood products - including 23,000 units of red cells - are transfused per year. His approaches to recovering the additional costs of leukoreduction have included discontinuing CMV serologic testing and better inventory management. Dr. Snyder estimated that the incremental net cost after the cost recoveries mentioned above for conversion from 30% to 100% leukoreduced blood products was about 3.8% of his total blood bank budget. Since universal leukoreduction was instituted at his institution, febrile reactions to blood products have decreased from about 10 per month to less than one per month.

Dr. Walter Dzik began his remarks by establishing the distinction between product safety, such as that provided by leukoreduction, and transfusion safety, which addresses all processes between collection from the donor to infusion into the recipient. He emphasized the need to assure the integrity of the entire transfusion process, and not just the product transfused. He then stated that the generally accepted indications for leukoreduction apply to only about 20% of transfusion recipients, and he proposed that selective application of technology such as leukoreduction was an appropriate strategy to assure good medical care. He noted that some proposed benefits of leukoreduction that might apply to all patients have not yet been conclusively demonstrated. He concluded by expressing his concern that a mandate for universal leukoreduction would have a negative effect on ongoing and proposed studies that address unresolved questions about leukoreduction itself, and about the scope of its benefits.

Dr. James AuBuchon spoke directly to the issue of universal versus selective leukoreduction. He proposed that the reduction in febrile transfusion reactions under universal leukoreduction would be minimal because most patients sensitized to leukocyte reactions are already receiving leukoreduced blood under the selective policy, and because leukocyte sensitization is not the

only cause of a febrile transfusion reaction. He noted that at his institution less than 10% of patients referred for treatment of leukemia have ever been transfused before. He stated that hidden costs of leukoreduction, such as quality control and loss of certain donor groups, might account for the twofold variation in the current charge by suppliers to hospital blood banks for this service. Dr. AuBuchon used Canadian and United Kingdom data to estimate that universal leukoreduction would add about a half a billion dollars annually to health care costs in this country. At his own institution, he estimated that universal leukoreduction would add 20% to his blood acquisition costs, above a recent 10% increase from his supplier. He suggested that other uses for this money, such as support for a hospital transfusion safety officer, would be of greater benefit.

Dr. S. Gerald Sandler began by expressing concern that adoption of universal leukoreduction would compromise ongoing studies of the technology. He cited the introduction of frozen-thawed-deglycerolized red cells in the 1960s, and the subsequent abandonment of this practice, as a precautionary precedent whenever the adoption of a new and incompletely evaluated technology is under consideration. He asked if there was an urgent public health issue that required a judgement on the issue of universal leukoreduction while uncertainties about some of its benefits remained. He objected to the mandate that would require him to fill a physician's order with a product more expensive than the one the physician had ordered, and he suggested an analogy between this mandate and a theoretical mandate that a more expensive, but not necessarily more beneficial, radiological procedure be performed than the one a physician had ordered. He suggested that new and controversial technologies be paid for by those who favor their use, rather than by a mandate that spreads the cost of their use over the entire health care system.

Dr. Paul Ness argued that selective leukoreduction policies could not assure that all individuals who would benefit from leukoreduction would receive leukoreduced products. One source he quoted was a multicenter study of leukoreduction in which 73% of patients who presented for treatment of acute leukemia had had a non-protocol transfusion within two weeks of study entry. For this reason, he suggested that a policy of selective leukoreduction does not meet the public expectation that the entire transfusion process be as safe and accurate as possible. He suggested that the three consensus indications for leukoreduction, namely reduced febrile transfusion reactions, reduction of alloimmunization, and reduced exposure to cell-associated pathogens, were sufficient by themselves to justify universal leukoreduction, and that the potential of universal leukoreduction to avoid unintended patient exposure to non-leukoreduced blood provided additional justification.

Dr. Blajchman stated that the need in medicine to make decisions based on available rather than complete evidence had not previously stopped medical research. He cited early studies of tuberculosis therapy, and ongoing studies of leukoreduction in Canada, to support this statement. He acknowledged the difficulty of performing cost-effectiveness analyses with the available data, but he presented an analysis favorable to universal leukoreduction that was based on the number of patients needed to treat in order to benefit a single patient. He concluded that the available scientific evidence is sufficient to support universal leukoreduction, and that the real but understated issue in the debate over this policy is money rather than science.

Dr. Vamvakas commented that the three generally accepted indications for leukoreduction had been demonstrated in a small subset of individuals who receive transfusion, and the extrapolation of these benefits to the transfused population as a whole was without empiric support. He felt that the argument for universal leukoreduction centers more on the issue of immunomodulation, on which there is agreement that current data is inconclusive, than on cost. His final comment was that if medical care is not available to a segment of the population, one has to wonder whether universal leukoreduction is the appropriate thing to do to advance medical care for Americans.

In the public comment period, the first speaker was Ms. Jacquelyn Frederick of the American Red Cross (ARC). She called on the FDA to mandate the implementation of universal leukoreduction. She stated that 77% of the red blood cells currently distributed by ARC are leukoreduced. She estimated that leukoreduction adds about \$30.00 to the cost of a unit of blood.

Dr. Celso Bianco of America's Blood Centers (ABC) stated that there was a diversity of views on the issue of universal leukoreduction within his organization, and he requested that decisions on this matter should be deferred to the local level. Dr. Bianco called for adequate reimbursement for all blood safety measures, and he outlined the initial response of ABC to the FDA Guidance on Leukoreduction that was released on January 23, 2001. He specifically raised issues related to testing potential donors for sickle hemoglobinopathies. There was discussion following his remarks on the potential impact that universal leukoreduction might have on the availability of blood from donors with rare blood types because it could exclude blood donors with sickle hemoglobinopathies

Dr. Jeffrey McCullough of the University of Minnesota cited the need in medicine to make decisions on the basis of incomplete information. He spoke in favor of universal leukoreduction on the basis of the three commonly accepted indications for this procedure, and on the basis of the currently available evidence for an immunomodulatory effect of blood transfusion.

Mr. Stephen Binyon of Baxter Healthcare Corporation, Mr. James O'Connor of HemaSure, Inc., Mr. Samuel Wertham of Pall Corporation, and Mr. Jeffrey Miripol of Terumo Corporation spoke in favor of universal leukoreduction and to emphasize the commitment of the organizations they represented to meet anticipated market demand for their leukoreduction products. In this segment of the public comment period, Mr. Staats Abrams of Roper Starch Worldwide presented the results of a telephone poll that elicited support for universal leukoreduction; Dr. Piliavin took issue with the methodology of this poll. Also, Ms. Nancy Chance of Riverview Hospital in Noblesville, IN described her favorable experience with instituting universal leukoreduction in a community hospital setting.

Dr. Ronald Sacher of the Hoxworth Blood Center in Cincinnati spoke on behalf of the University HealthSystem Consortium, which had surveyed its membership and convened an expert panel to review this issue in October 2000. The survey respondents and panelists opposed universal leukoreduction by ratios of approximately two to one. Dr. Lawrence Petz of the University of California spoke on behalf of the American Hospital Association. He stated his view that the issue of whether any deleterious immunomodulatory effects of allogeneic transfusion can be

prevented or ameliorated by blood transfusion remains unresolved. He quoted a letter opposing universal leukoreduction that he and 30 other transfusion medicine physicians had signed and had published in the journal Transfusion.

Next, Dr. Dennis Goldfinger of Cedars-Sinai Medical Center spoke in favor of universal leukoreduction, and he cited a letter supporting universal leukoreduction that he and 7 other transfusion medicine physicians had signed and had published in Transfusion.

Dr. Neil Blumberg of the University of Rochester reviewed clinical and pre-clinical evidence in support of his view, which he characterized as a minority one, that leukoreduction can reduce or ameliorate the clinical or laboratory manifestations of allogenic or autologous transfusion-induced immunomodulation. He pointed out that even a small relative reduction in postoperative morbidity or mortality due to leukoreduction of blood components would have a substantial public health impact because of the large number of individuals, for example cardiac surgery patients, who receive blood each year.

Ms. Mary Foss and Dr. S. Breannan Moore of the Mayo Clinic discussed the costs of implementing universal leukoreduction at their institution, which transfuses about 44,000 units of red cells and 54,000 platelet unit equivalents per year. Ms. Foss said her institution's baseline leukoreduction rates of 17% for red cells and 70% for platelets. They produce 56% of the red cells they use and 71% of the platelets. Ms. Foss estimated that they would pay an extra \$28.00 for each leukoreduced unit they purchased from the American Red Cross, and an extra \$24.00 for each leukoreduced unit they produced on their own; the total incremental cost to their institution would be \$1.2 million per year. Dr. Moore stated his view that the current debate about leukoreduction was of necessity about money. He cited the currently available evidence suggesting that leukoreduction may reduce postoperative infection, and suggested that, if this evidence can be confirmed, there could be a very beneficial effect of leukoreduction. His advice to the Advisory Committee was that a decision on universal leukoreduction should be deferred until studies currently in progress to test this hypothesis could be completed.

Dr. Merlin Sayers of Carter BloodCare spoke about potential vulnerabilities of the blood supply that might be accentuated by a policy of universal leukoreduction. He expressed concern about the limited competition among suppliers of leukoreduction devices and support services, including patent licensures, and the correspondingly limited forces to constrain the prices of these products. He also expressed concern about the effect in this limited market of a recall of leukoreduction devices on the availability of devices remaining on the market to meet demand for blood.

Next, Mr. David Cavanaugh of the Committee of Ten Thousand, Mr. Richard Vogel of the Hemophilia Federation of America, Mr. Patrick Collins of the National Hemophilia Foundation, and Mr. Jason Bablak of the Immune Deficiency Foundation all spoke in favor of universal leukoreduction. The meeting was then adjourned for the evening.

The meeting resumed the following morning with a presentation by Dr. Jong-Hoon Lee of the FDA position on leukoreduction. Dr. Lee reviewed in detail the Guidance to Industry on leukoreduction that was posted on the FDA web site on January 22, 2001. The Guidance recommends but does not mandate leukocyte reduction.

There were several comments from the Advisory Committee and from the public about technical aspects of the Guidance. Dr. Lee and later Dr. Epstein both emphasized that the Guidance was issued as a Draft for Comment, that comments received would be carefully reviewed, and that, even after the Guidance was revised and reissued under Good Guidance Practice, it would not have the force of regulation.

In the discussion that followed, the Advisory Committee developed a set of statements on which it felt there was consensus. These are

1. With few exceptions, prestorage leukoreduced blood is not inherently dangerous to the recipient.
2. There is agreement that leukoreduction is beneficial for some patients by reducing the number of febrile events, CMV transmission, and alloimmunization.
3. The evidence is not conclusive that leukoreduction reduces postoperative infections or reduces malignancy in unrecognized immunodeficient patients.
4. The likely benefits of universal leukoreduction include averting consequences of failure to identify those who may require leukoreduced products and reducing the likelihood of administration of incorrect blood products.
5. Areas of contention regarding universal leukoreduction include cost, effect on supply, compromising future investigations, and regulatory burden.

Dr. Piliavin then proposed, and Dr. Busch seconded, the following motion:

The Advisory Committee should reconsider the issue of universal leukoreduction in one year.

After discussion of this issue, the vote was 2 for, 11 against, 1 abstain, Chairman not voting except to break a tie. The motion was defeated

Dr. Penner then proposed, and Dr. Gilcher seconded, the following motion:

1. **Universal leukoreduction should be implemented as soon as feasible.**

After discussion of this issue, the vote was 10 for, 3 against, 1 abstain, Chairman not voting except to break a tie. The motion was approved.

Dr. Penner then proposed, and Dr. Hoots seconded, the following motion:

2. **In regard to universal leukoreduction, the Advisory Committee is concerned about the availability of blood, and the resources necessary to implement universal leukoreduction. For these reasons, the Advisory Committee recommends that the actions of the Department of Health and Human Services should strive to**
 - a. **minimize the impact on supply,**
 - b. **assure adequate funding for this effort,**
 - c. **issue a regulation to implement universal leukoreduction that addresses these concerns, and**
 - d. **report to the Advisory Committee on a regular basis the progress toward these goals.**

After discussion of this issue, the vote was for 14 for, 0 against, 0 abstain, Chairman not voting except to break a tie. The motion was approved.

Mr. Walsh then proposed, and Dr. Haas seconded, the following motion:

3. **The Advisory Committee recommends that the Secretary appoint a representative of the Health Care Financing Administration as a non-voting government representative to the Advisory Committee.**

After discussion of this issue, the vote was for 14 for, 0 against, 0 abstain, Chairman not voting except to break a tie. The motion was approved.

Dr. Hoots then proposed, and Dr. Davey seconded, the following motion:

4. **Given the unresolved scientific issues in the field, the Advisory Committee supports continuing research on the effectiveness of universal leukoreduction.**

After discussion of this issue, the vote was for 14 for, 0 against, 0 abstain, Chairman not voting except to break a tie. The motion was approved.

Dr. Snyder then proposed, and Mr. Walsh seconded, the following motion:

5. **In the above resolutions, the word "leukoreduction" is intended to mean prestorage leukoreduction, and the resolutions refer to non-leukocyte cellular blood components.**

After discussion of this issue, the vote was for 14 for, 0 against, 0 abstain, Chairman not voting except to break a tie. The motion was approved.

After a brief discussion of future agenda items, the meeting was adjourned at 12:07 PM. These minutes were approved by the Chairman, Dr. Caplan, on February 1, 2001.